MRI Evaluation of Cartilage Maturation

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1. Introduction

Various quantitative MRI (qMRI) techniques hold potential in evaluating the extracellular matrix of articular cartilage. In order to apply these techniques in evaluating tissue maturation and to correctly interpret the results it is necessary to understand the structural and compositional changes that occur within growing cartilage. Also, understanding the MRI appearance of cartilage, as verified by histological correlation of tissue content, may help in preventing the pitfalls underlying in the frequent use of immature animal cartilage as a model for human articular cartilage.

This paper summarizes the current understanding of cartilage remodelation during maturation, and the available MRI techniques for its evaluation are reviewed. Selected MRI results of cartilage development are presented with parallel histology in order to interpret the MRI findings.

2. Mature articular cartilage

Adult cartilage is composed of water (60-80% by weight), relatively few chondrocytes (1%), and hydrophilic proteoglycan aggregates (4-7%) enforced by a network of collagen fibrils (15-22%) (1). The proteoglycan concentration increases from surface to deep cartilage (2) while collagen concentration behaves in an inverse manner (3). Benninghoff initially reported the complex structure of the collagen network with three distinct zones from the articular surface to deep tissue: the tangential zone (5-15% of total cartilage thickness) has collagen fibrils aligned along the articular surface, arcading into the transitional zone (1-15%) where fibrils have a more or less random orientation, and finally arrange to become perpendicular to the subchondral bone in the radial zone (70-90%) where fibrils become anchored to the underlying bone (4).

To accommodate the varying loading conditions, topographical variation of structure and composition of cartilage exists, resulting in different mechanical properties in different areas of the joint (5). Thus, the ultimate goal in the development of MRI techniques is not only to estimate the construction of the extracellular matrix but to predict the function of the tissue in order to evaluate its prerequisites to accomplish the demanding task of energy absorption and dissipation during locomotion.

3. Immature articular cartilage

While the structure and composition of adult articular cartilage has been known for several decades, only recent advances in histological techniques have provided insight into the changes taking place in the architecture of maturing cartilage. Enhanced polarized light microscopy (ePLM) has recently provided means to study the fiber angle and anisotropy (parallelism) of collagen fibrils (6,7). Fourier Transform Infrared Imaging Spectroscopy (FT-IRIS), on the other hand, enables the assessment of the spatial variation of collagen and proteoglycan contents (8). More conventional techniques, namely the densitometry of stained proteoglycans (9) and biochemical assays (10,11) supplement the aforementioned methods in revealing tissue changes in the course of maturation.

In the developing joint, bone ends are initially formed of epiphyseal hyaline cartilage, and become ossified with age apart from the layer of articular cartilage. Unlike adult articular cartilage, postnatal human cartilage is lacking an organized collagen network. Collagen fibrils of young porcine cartilage (4 months) are reported to exhibit a preferential tangential arrangement even in deep parts of the tissue, yet the order of anisotropy in the radial zone is lower than in adult cartilage (12). In immature tissue, several additional histological zones (up to seven in total) have been observed in juvenile animal tissue (7,13-16), and these are possibly related to zones of high cell density where collagen fibrils curve around the chondrocytes (7,16). These tissue areas most likely represent the cartilaginous epiphysis which will eventually become bone. Both the spatial distribution and content of collagen modulates during the development of cartilage, reaching its highest content at maturity (12). On the contrary, a significant decrease in proteoglycan content has been reported with maturation in rat cartilage (17). The overall solid content slowly increases with maturation (i.e. water content decreases) (18). The significant increase of confined compression modulus and the decrease in hydraulic permeability of fetal to adult bovine cartilage are primarily associated to the development of the collagen component (18). Thus, during skeletal maturation towards the final cartilage phenotype

the tissue structure and composition go through phases of significant remodelation that are dramatically reflected in the functional properties of the tissue.

4. qMRI for cartilage composition and structure

Several qMRI techniques have been tested in assessing the collagen component of cartilage. T_2 relaxation time was initially the parameter of interest due to the distinct and unique MRI appearance of cartilage on T2-weighted MR images (19). Cartilage T_2 is sensitive to the architecture and organization of collagen fibrils (16,20,21), but also dependent on the collagen content (22,23) and water content of the tissue (24,25). Conflicting reports exist on the influence of cartilage proteoglycans on T_2 relaxation (26,27). While T_2 relaxation time may not be specific to collagen, its spatial variation and laminar appearance is indisputably dependent on the arrangement of the collagen fibrils in the B_0 field due to the orientation dependent dipolar interaction of collagen associated water, known as the "magic angle effect". The in vivo application of T_2 is challenged by the varying orientation of the curved articular surfaces that lead to an orientation dependent variation of T_2 even in normal cartilage. Yet, promising in vivo results have been reported in the recent years (28). In addition to T_2 relaxation, also other MRI parameters have shown a degree of sensitivity on the collagen component of cartilage. The collagen matrix is the predominant determinant of magnetization transfer effects in cartilage, however, it is not very sensitive to changes in the physiological range (29,30). Diffusion tensor imaging of cartilage may enable the determination of the collagen fibril arrangement (31). Similar to T_2, ^2H and ^{23}Na quadrupolar splittings depend on the direction of interaction and the B_0 field and can be used to study the orientation of fibrils in different cartilage zones (32).

For the estimation of the proteoglycan content of cartilage, the delayed Gadolinium Enhanced MRI of Cartilage (dGEMRIC) technique has been widely used. The technique utilizes the cationic contrast agent Gd-$DTPA^{2-}$ which distributes in inverse relation to the fixed negative charge of the glycosaminoglycans of proteoglycans in order to modulate the T_1 relaxation time of the tissue (33). The technique has been validated both for bulk tissue and spatially (34,35), and has been applied in several in vitro and in vivo studies (36-45). $T_{1\rho}$ mapping, i.e. T_1 relaxation in the rotating frame, is another candidate for evaluating cartilage proteoglycans (46). It shows a high correlation with biochemical proteoglycan measures (47,48) and initial in vivo testing has been reported (49,50). The specificity of $T_{1\rho}$ for cartilage proteoglycans, however, is hindered by its dependence on residual dipolar interaction related to collagen orientation (51). Finally, Na-MRI is a method that can be used to quantify the amount of sodium ions attracted by the fixed negative charge of cartilage proteoglycans (52). The technique is sensitive and specific in detecting small changes in proteoglycan concentration (53) and has been tested in an in vivo model (54).

Mechanical properties of cartilage have been successfully related to dGEMRIC, T_2 and $T_{1\rho}$ (38,39,43,55-58). The correlations between moduli and MRI parameters has been high at best, and the techniques have reproduced the topographical variation in mechanical properties across the joint (39,59). The correlations, however, tend to be inferior when examining pathologic tissue.

5. qMRI of the developing extracellular matrix

In the wake of microscopic discoveries of cartilage maturation, MRI has shown its potential in assessing cartilage development. T_2-weighted signal is reported to decrease with maturation, and the homogeneous appearance of the cartilaginous epiphysis at the very early childhood is reported to change to a laminated appearance resembling that of mature cartilage (60,61). With reference to the findings presented in section 3, the signal decrease is likely caused by the remodelation of the collagen network towards an anisotropic structure and by the general increase in solid content (collagen and proteoglycans).

T_2 relaxation time mapping has shown promise in revealing the diverging cartilage structure. The additional zones observed with polarized light microscopy correlate well with the depth-wise variation of T_2 relaxation time (7,13,16). These structures frequently exhibit consecutive zones of low and high collagen anisotropy, and they are manifested in MRI as laminae of long and short T_2 relaxation times, respectively (Fig. 1A). The probable mechanisms for the T_2 elevation is the reduced dipolar interaction due to lower collagen anisotropy and increased water content due to hypercellularity (16). Complicated collagenous structures in the young canine humeral head has been revealed: fibrils in central areas exhibit a tri-laminar appearance while the structure becomes more complicated when moving to the peripheral area of the joint with different loading conditions (7). This could possibly explain the higher T_2 relaxation time observed in non-weight-bearing cartilage as compared to weight-bearing tissue in the femoral compartment of the pediatric knee (62). A significant increase in ^2H and ^{23}Na quadrupolar splitting with age has been observed, providing another means to study the order of collagen anisotropy with maturation (63).

dGEMRIC has been used to investigate the proteoglycan content in the course of cartilage development in a single study (64). Histology of superficial cartilage in adult humans showed a lower proteoglycan content as

opposed to immature bovine and immature porcine cartilage. dGEMRIC revealed a similar trend, however, the difference was not statistically significant. A poor correlation between dGEMRIC and histological quantitation of stained proteoglycans has been revealed in the deep parts of immature cartilage (35,64). This is possibly related to the high cellularity of deep juvenile cartilage which infringes the single compartment assumption made in the dGEMRIC technique or high tissue permeability in these tissue zones that could restrict the accumulation of the contrast agent (35). Nonetheless, several other studies have shown the capability of dGEMRIC in revealing subtle changes in the PG content of cartilage (Fig. 1B), and when used with caution it is one of the most potential techniques in revealing maturation related proteoglycan changes in cartilage.

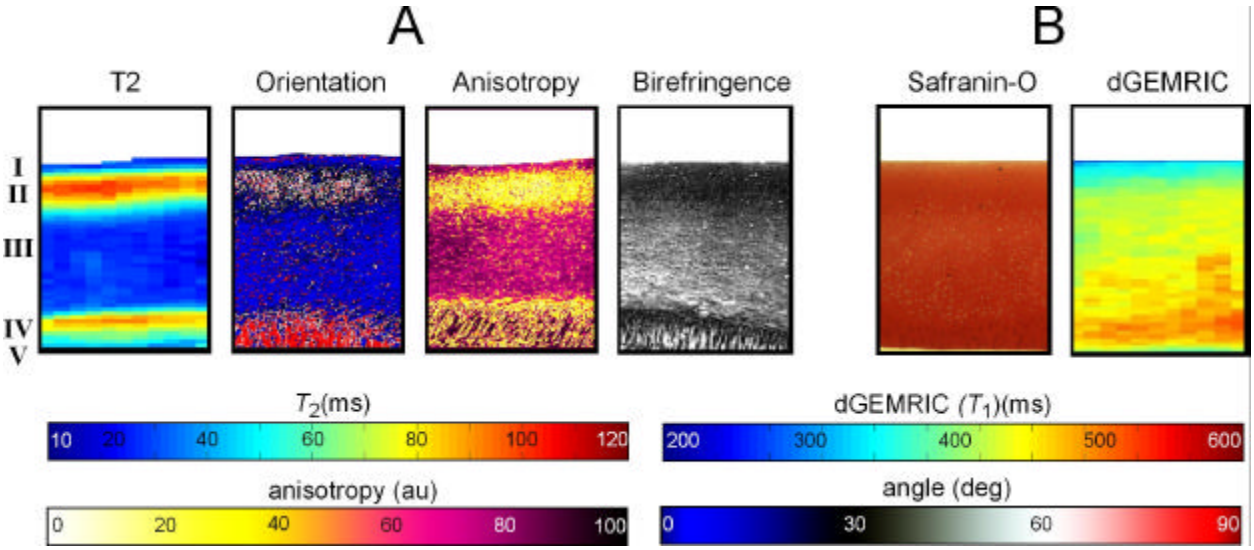

Figure 1: For a sample of juvenile cartilage imaged at 9.4T (cartilage surface is towards the top of the page), **A:** T_2 map and ePLM images (orientation, anisotropy and birefringence); **zone I**: superficial cartilage with collagen fibrils arranged along the cartilage surface, and a concomitant short T_2 relaxation time; **zone II**: arcading collagen fibrils with low anisotropy together with a long T_2; **zone III**: anisotropic collagen fibrils with tangential arrangement (as in zone I) and short T_2 relaxation time; **zone IV**: anisotropic collagen arrangement and prolonged T_2; **zone V**: radial collagen fibrils with some degree of anisotropy and short T_2 relaxation time. **B:** safranin-O stained section and respective dGEMRIC map: proteoglycan content increases from superficial to deep cartilage and this variation is also visualized by dGEMRIC. (Image courtesy of Mikko Nissi, University of Kuopio)

Surgically produced repair tissue, such as that resulting from autologous chondrocyte transplantation (ACT), is analogous to postnatal articular cartilage in the sense that it lacks the three-dimensional arrangement of collagen fibrils. dGEMRIC and T_2 mapping have been used to evaluate ACT repair tissue in humans (36,37,65). dGEMRIC revealed PG replenishment in ACT grafts. The repair tissue, however, showed an elevated T_2 relaxation time without a distinct laminar appearance, which may be explained by the lack of the three-dimensional collagenous architecture. T_2 mapping has the potential to show emerging arrangement of collagen in repair tissue, however, it is unlikely that the tissue develops such a structure any quicker than in the age of skeletal maturation. Therefore long term follow-up qMRI studies are required.

Another study used various MRI parameters to evaluate regenerated tissue in an animal model of spontaneous repair (66). Repair tissue showed a trend toward low PG content, as assessed by dGEMRIC, and low T_2 values likely resulting from the fibrous cartilage structure as verified by polarized light microscopy. T_1 and diffusion measurements were not particularly sensitive in differentiating regenerated tissue from normal cartilage, however, the number of samples in the study was very small and prevented from running statistical tests.

6. Summary

Developing cartilage shows dramatic changes in the extracellular matrix in course of time. qMRI techniques are very promising in the nondestructive assessment of the maturation related changes in the macromolecular constituents of cartilage. To date, T_2 mapping and dGEMRIC have been used in revealing structural

changes in the three-dimensional collagen matrix and proteoglycans, respectively. Several other MRI parameters have the potential to further characterize cartilage maturation and their applicability remains to be shown.

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